REMARKS

Applicants thank the Examiner for his review of the instant application. For the reasons stated below, the rejections of the presently pending claims are respectfully traversed. Claims 6-8 and 11-17 are presented for examination.

Status of the Claims

Applicants mailed an Amendment After Final Office Action on September 23, 2005. In that Amendment, Applicants canceled Claims 4-5 without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application. Applicants also amended Claim 12 to depend from Claim 6, rather than canceled Claim 4. The listing of the claims above repeat these amendments as it is not known if the previously filed Amendment After Final Office Action was entered.

Rejection Under 35 U.S.C. §101

The PTO maintains its rejection of pending Claims 6-8 and 11-17 under 35 U.S.C. § 101 as lacking utility for the reasons set forth in the previous Office Actions. The PTO states that the specification discloses that the PRO1753 polynucleotide is more highly expressed in esophageal tumor tissue as compared to normal esophageal tissue, and that Applicants have asserted the use of the molecule for diagnosis. However, the PTO rejects this utility "because the skilled artisan recognizes that protein levels are not always consistent with mRNA levels." *Final Office Action* at 3.

Applicants incorporate by reference their previously submitted arguments, including those made in the Appeal Brief, and for the reasons of record assert that the specification contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented and therefore must be taken as sufficient to satisfy the utility requirement of 35 U.S.C. § 101. Applicants also submit that for reasons of record, the PTO has not met its burden of providing evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility. However even if the PTO has met its initial burden, Applicants' rebuttal evidence previously submitted and additional evidence submitted herewith is sufficient to prove

that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true. As stated previously, Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not absolute certainty.**

Substantial Utility

Summary of Applicants' Arguments and the PTO's Response

Applicants' asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO1753 polypeptide is expressed at least two-fold higher in esophageal tumor tissue as compared to normal esophageal tissue;

2. Applicants assert that it is well-established in the art that a change in the level of mRNA for a particular protein, *e.g.* an increase, generally leads to a corresponding change in the level of the encoded protein, *e.g.* an increase;

3. Given the differential expression of the PRO1753 mRNA in esophageal tumors as compared to normal esophageal tissue, it is more likely than not that the PRO1753 polypeptide is also differentially expressed in esophageal tumors as compared to normal esophageal tissue, making the claimed polypeptides useful as diagnostic tools, alone or in combination with other diagnostic tools.

Applicants understand the PTO to be making two arguments in response to Applicants' asserted utility:

1. The PTO challenges the reliability of the evidence reported in Example 18, stating that "the significance or relevance of the disclosed PRO1753 mRNA expression in relation to cancer diagnosis or treatment is unknown," citing Hu *et al.* for support;

2. The PTO argues that "protein levels are not always consistent with mRNA levels and that protein levels are not predictable from the mRNA expression levels," citing Haynes *et al.* (Electrophoresis, (1998) 19(11):1862-71) Gygi *et al.* (Mol. and Cell. Bio., (1999) and Hancock (J. Proteome Res., (2004) 3(4):685).

Applicants respectfully submit that in light of all of the evidence, the PTO's arguments are not adequate to support the utility rejection of the claimed invention under 35 U.S.C. § 101.

Applicants have established that the Gene Encoding the PRO1753 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue

Applicants submit that the gene expression data provided in Example 18 of the present application are sufficient to establish that the PRO1753 gene is differentially expressed in esophageal tumors compared to normal esophageal tissue, and is therefore useful as a diagnostic tool for cancer, specifically esophageal cancer.

Applicants previously submitted a first Declaration of J. Christopher Grimaldi, an expert in the field of cancer biology. This declaration explains the importance of the data in Example 18, and how differential gene and protein expression studies are used to differentiate between normal and tumor tissue.

In paragraph 5 of his declaration, Mr. Grimaldi states that the gene expression studies reported in Example 18 of the instant application were made from pooled samples of normal and of tumor tissues. Mr. Grimaldi explains that:

> The DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues. Data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual. That is, the detection of variations in gene expression is likely to represent a more generally relevant condition when pooled samples from normal tissues are compared with pooled samples from tumors in the same tissue type. *First Grimaldi Declaration* at ¶ 5 (emphasis added).

In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or under-expressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. Thus, the results of Example 18 reflect at least a two-fold difference between the pooled normal and tumor samples. This detected differential expression in pooled tumor samples compared to pooled normal samples represents a more generally relevant result compared to differential expression detected in samples from a single individual. He also states that the results of such gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal," thus establishing their reliability. He further states that if a "difference is detected, this

indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor."

In response, the PTO relies on an article by Hu, *et al.*, arguing that "the significance or relevance of the disclosed PRO1753 mRNA expression in relation to cancer diagnosis or treatment is unknown." *Final Office Action* at 9.

In addition to the reasons articulated in Applicants' arguments of record, which Applicant incorporates by reference, the PTO's reliance on Hu is also misplaced because Applicants are not relying on microarray data as discussed in Hu:

> In any microarray experiment, thousands of genes may demonstrate statistically significant expression changes, but only a fraction of these may be relevant to the study. *Hu* at 405, left column, first paragraph (emphasis added).

Instead, Applicants are relying on a more accurate and reliable method of assessing changes in mRNA level, namely quantitative PCR analysis. In a recent study by Kuo *et al.*, (Proteomics 5(4):894-906 (2005)), the authors used microarray analysis combined with proteomic analysis using two-dimensional gel electrophoresis to examine changes in gene expression in leukemia cell lines. The authors report that "[c]omparison of microarray and proteomic expression profiles showed poor correlation. Use of more reliable and sensitive analyses, such as reverse transcriptase polymerase chain reaction [RT-PCR], Western blotting and functional assays, on several genes and proteins, nonetheless, confirmed that there is indeed good correlation between mRNA and protein expression." *Kuo et al.* at Abstract (emphasis added) (attached as Exhibit 1). Thus, even if accurate, Hu's statements regarding microarray studies are not relevant to the instant application which does not rely on microarray data.

Moreover, Hu is silent regarding the reliability of pooled samples, and whether or not differential expression in pooled samples are susceptible to disease-independent differences between samples. The PTO's concern that "it is unknown if the PRO1753 transcript differences are disease-dependent or disease-independent" is addressed by the statement in the first Grimaldi Declaration that "DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues. Data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual." *First Grimaldi Declaration* at ¶ 5. Hu provides no reason to expect that differential expression in pooled samples is attributable to disease-independent differences between samples. Thus, Hu does not provide a basis for

doubting Applicants' differential expression data. As such, there is no evidence that one skilled in the art would question whether the differential expression of PRO1753 mRNA in pooled samples was disease-dependent or disease-independent.

In conclusion, Applicants submit that the evidence reported in Example 18, supported by the first Grimaldi Declaration, establish that there is at least a two-fold difference in PRO1753 mRNA between esophageal tumors as compared to normal esophageal tissue. Thus, any challenge to the sufficiency of the data with respect to the utility of the nucleic acid is inappropriate. Therefore, the only issue which remains is whether the data in Example 18 regarding differential expression of the PRO1753 mRNA are reasonably correlated with differential expression of the PRO1753 polypeptide such that the claimed polypeptides have utility as diagnostic tools as well. As discussed below, even if the PTO has established a reasonable doubt regarding Applicants' assertion that they are reasonably correlated, Applicants' overwhelming rebuttal evidence is more than sufficient to establish that changes in mRNA level lead to corresponding changes in protein level.

The PTO's Evidence is Not Relevant to Determining Whether a Change in mRNA Level for a Particular Gene lead to Corresponding Change in the Level of the Encoded Protein

Applicants turn next to the second portion of their argument in support of their asserted utility – that it is well-established in the art that a change in the level of mRNA encoding a particular protein generally leads to a corresponding change in the level of the encoded protein; given Applicants' evidence of differential expression of the mRNA for the PRO1753 polypeptide in esophageal tumors, it is likely that the PRO1753 polypeptide is also differentially expressed; and proteins differentially expressed in certain tumors have utility as diagnostic tools.

In response to Applicants' assertion, the PTO cites Haynes *et al.* (Electrophoresis, (1998) 19(11):1862-71) Gygi *et al.* (Mol. and Cell. Bio., (1999) and Hancock (J. Proteome Res., (2004) 3(4):685) for support of its argument that "protein levels are not always consistent with mRNA levels and that protein levels are not predictable from the mRNA expression levels." *Final Office Action* at 9.

Applicants have previously discussed at length why the Haynes, Gygi and Hancock references are not relevant to the issue of whether changes in mRNA level for a particular gene

lead to changes in protein level. Applicants incorporate by reference the previous arguments, including those made in their appeal brief, and will not repeat them here.

However, in an attempt to illustrate why references which relate to static global levels of mRNA and protein across different genes are not relevant to this issue, Applicants offer the following illustration and analogy with the understanding that like all illustrations and analogies, they are not perfect and therefore do not represent any admissions or binding statements regarding Applicants' disclosure or invention.

Haynes and Gygi discuss whether there is a correlation between the static level of mRNAs and proteins globally, *i.e.* across different genes. This is equivalent to conducting a hypothetical Experiment 1, where a particular cell type has 100 copies of mRNA for gene X, 200 copies of mRNA for gene Y, and 400 copies of mRNA for gene Z. If there is a global correlation between static mRNA levels and protein levels across genes, the ratio of the amount of proteins X:Y:Z would be approximately 1:2:4. This is essentially what the cited references examined.

In contrast, Applicants are relying on a correlation between changes in mRNA level for a particular gene leading to a corresponding change in the level of the encoded protein. For example, in hypothetical Experiment 2, if gene X has 100 copies of mRNA per cell in condition A (*e.g.* normal), and 200 copies of mRNA for gene X in condition B (*e.g.* tumor), the ratio of the amount of protein X in condition A:B would be approximately 1:2, such that there is a correlation between the change in the level of mRNA and protein for a particular gene.

The PTO argues that because there is no correlation between static levels of mRNA and protein across genes, as illustrated by Experiment 1, one of skill in the art would not expect an increase or decrease in the amount of mRNA for a particular gene to result in a corresponding change in the amount of the encoded protein, as illustrated in Experiment 2. This is simply wrong.

For example, Haynes reports that the amount of protein produced by similar levels of mRNA varied by as much as fifty-fold, and that similar amounts of protein were sustained by amounts of mRNA that varied by as much as forty-fold. *Haynes* at 1863, first full paragraph. Based on these results, Haynes concludes that "protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript." *Id.*

This is analogous to a finding that on one gallon of gas, a hybrid car can travel 70 miles but a large truck can only travel 5 miles, or that to travel 70 miles, a hybrid car requires 1 gallon of gas, but a large truck requires 14 gallons. That is to say, there are many things which affect the fuel efficiency of an automobile. Based on these observations, one could conclude that given the lack of correlation between the amount of gas in an automobile and the distance it travels, one cannot predict how far an automobile will travel based on the amount of gas in the tank.

Even if true, Haynes' data and conclusions are irrelevant to Applicants' assertion, which is that increasing or decreasing the amount of mRNA for a particular gene will result in a corresponding increase or decrease in the amount of the encoded protein. This is analogous to increasing or decreasing the amount of gas in an automobile – it will travel farther if you add more gas, and not as far with less. The fact that there are many things which affect fuel efficiency and therefore you cannot predict how far and automobile will travel without knowing if it is a hybrid or a large truck is irrelevant – both a hybrid and a truck travel farther on more gas, and not as far on less.

Applicants emphasize, and the PTO will recognize, that these are simplified illustrations to demonstrate the difference between the two issues being examined. However, these illustrations make clear that even if there is no correlation in the first experiment looking at static levels of mRNA and protein across genes, there can still be a correlation between changes in mRNA and protein for a particular gene as examined in the second experiment. As these illustrations make clear, the PTO's evidence simply is not relevant to answering the question of whether it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true.

Applicants' Evidence Establishes that a Change in mRNA Level for a Particular Gene lead to Corresponding Change in the Level of the Encoded Protein

In support of the assertion that changes in mRNA are positively correlated to changes in protein levels, Applicants previously submitted a copy of a second Declaration by J. Christopher Grimaldi, a copy of the declaration of Paul Polakis, Ph.D., excerpts from the Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) and (4th ed. 2002), excerpts from the textbook, Genes VI, (Benjamin Lewin, Genes

VI (1997)), a reference by Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004, and a reference by Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002). The details of the teachings of these declarations and references, and how they support Applicants' asserted utility, are of record and will not be repeated here.

Applicants submit herewith a copy of a second Declaration by Dr. Polakis (attached as Exhibit 2) that presents evidentiary data in Exhibit B. Exhibit B of the Declaration identifies 28 gene transcripts out of 31 gene transcripts (i.e., greater than 90%) that showed good correlation between tumor mRNA and tumor protein levels. As Dr. Polakis' second Declaration says "[a]s such, in the cases where we have been able to quantitatively measure both (i) mRNA and (ii) protein levels in both (i) tumor tissue and (ii) normal tissue, we have observed that in the vast majority of cases, there is a very strong correlation between increases in mRNA expression and increases in the level of protein encoded by that mRNA." Accordingly, Dr. Polakis has provided the facts to enable the PTO to draw independent conclusions.

The case law has clearly established that in considering affidavit evidence, the Examiner must consider all of the evidence of record anew. *See in re Rinehart,* 531 F.2d 1084, 189 USPQ 143 (C.C.P.A. 1976); *In re Piasecki,* 745 F.2d. 1015, 226 USPQ 881 (Fed. Cir. 1985). "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument." *In re Alton,* 37 U.S.P.Q.2d 1578, 1584 (Fed. Cir. 1996), *quoting In re Oetiker,* 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992). Furthermore, the Federal Court of Appeals held in *In re Alton*, "We are aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner." *Id.* at 1583. Applicants also respectfully draw the PTO's attention to the Utility Examination Guidelines which state, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." *66 Fed. Reg. 1098, Part IIB (2001).*

In addition to the supporting references previously submitted by Applicants, Applicants submit the following references to further support the assertion that changes in mRNA levels generally lead to corresponding changes in the level of the encoded polypeptide.

In a comprehensive study by Orntoft *et al.* (Mol. Cell. Proteomics. 2002; 1(1):37-45) (previously submitted with IDS, attached hereto as Exhibit 3), the authors examined gene amplification, mRNA expression level, and protein expression in pairs of non-invasive and invasive human bladder tumors. *Id.* at Abstract. The authors examined 40 well resolved abundant known proteins, and found that "[i]n general there was a highly significant correlation ($p<0.005$) between mRNA and protein alterations. Only one gene showed disagreement between transcript alteration and protein alteration." *Id.* at 42, col. 2. The alternations in mRNA and protein included both increases and decreases. *Id.* at 43, Table II. Clearly, a correlation in 39 of 40 genes examined supports Applicants' assertion that changes in mRNA level generally lead to corresponding changes in protein level.

In a study by Wang *et al.* (Urol. Res. 2000; 28(5):308-15) (abstract attached as Exhibit 4) the authors report that down-regulation of E-cadherin protein has been shown in various human tumors. *Id.* at Abstract. In the reported study, the authors examined the expression of cadherins and associated catenins at the mRNA level in paired tumor and nonneoplastic primary prostate cultures. They report that "[s]ix of seven cases of neoplastic cultures showed moderately-to-markedly decreased levels of E-cadherin and P-cadherin mRNA. Similar losses of alpha-catenin and beta-catenin mRNA were also observed." *Id.* As Applicants' assertion would predict, the authors state that the mRNA measures showed "good correlation" with the results from protein measures. The authors conclude by stating that "this paper presents a coordinated down-regulation in the expression of E-cadherin and associated catenins at the mRNA and protein level in most of the cases studied." *Id.*

In a more recent study by Munaut *et al.* (Int. J. Cancer. 2003; 106(6):848-55) (abstract attached as Exhibit 5) the authors report that vascular endothelial growth factor (VEGF) is expressed in 64-95% of glioblastomas (GBMs), and that VEGF receptors (VEGFR-1, its soluble form sVEGFR-1, VEGFR-2 and neuropilin-1) are expressed predominantly by endothelial cells. *Id.* at Abstract. The authors explain that infiltrating tumor cells and newly-formed capillaries progress through the extracellular matrix by local proteolysis involving matrix metalloproteinases (MMPs). In the present study, the authors "used quantitative RT-PCR, Western blot, gelatin zymography and immunohistochemistry to study the expression of VEGF, VEGFR-1, VEGFR-2, sVEGFR-1, neuropilin-1, MT1-MMP, MMP-2, MMP-9 and TIMP-2 in

20 human GBMs and 5 normal brains. The expression of these MMPs was markedly increased in most GBMs with excellent correlation between mRNA and protein levels." *Id.* Thus, the results support Applicants' assertion that changes in mRNA level lead to corresponding changes in protein level.

In another recent study, Hui *et al.* (Leuk. Lymphoma. 2003; 44(8):1385-94 (abstract attached as Exhibit 6) used real-time quantitative PCR and immunohistochemistry to evaluate cyclin D1 mRNA and protein expression levels in mantle cell lymphoma (MCL). *Id.* at Abstract. The authors report that seven of nine cases of possible MCL showed overexpression of cyclin D1 mRNA, while two cases showed no cyclin D1 mRNA increase. *Id.* Similarly, "[s]ix of the seven cyclin D1 mRNA overexpressing cases showed increased cyclin D1 protein on tissue array immunohistochemistry; one was technically suboptimal." *Id.* The authors conclude that the study "demonstrates good correlation and comparability between measure of cyclin D1 mRNA ... and cyclin D1 protein." *Id.* Thus, this reference supports Applicants' assertion.

In a recent study by Khal *et al.* (Int. J. Biochem. Cell Biol. 2005; 37(10):2196-206) (abstract attached as Exhibit 7) the authors report that atrophy of skeletal muscle is common in patients with cancer and results in increased morbidity and mortality. *Id.* at Abstract. To further understand the underlying mechanism, the authors studied the expression of the ubiquitin-proteasome pathway in cancer patient muscle using a competitive RT-PCR to measure expression of mRNA for proteasome subunits C2 and C5, while protein expression was determined by western blotting. "Overall, both C2 and C5 gene expression was increased by about three-fold in skeletal muscle of cachectic cancer patients (average weight loss 14.5+/-2.5%), compared with that in patients without weight loss, with or without cancer. ... There was a good correlation between expression of proteasome 20Salpha subunits, detected by western blotting, and C2 and C5 mRNA, showing that increased gene expression resulted in increased protein synthesis." These findings support Applicants' assertion that changes in mRNA level lead to changes in protein level.

Maruyama *et al.* (Am. J. Patho. 1999; 155(3):815-22) (abstract attached as Exhibit 8) investigated the expression of three Id proteins (Id-1, Id-2 and Id-3) in normal pancreas, in pancreatic cancer and in chronic pancreatitis (CP). The authors report that pancreatic cancer cell lines frequently coexpressed all three Ids, "exhibiting good correlation between Id mRNA and

protein levels." *Id.* at Abstract. In addition, the authors teach that all three Id mRNA levels were expressed at high levels in pancreatic cancer samples compared to normal or CP samples. At the protein level, Id-1 and Id-2 staining was faint in normal tissue, while Id-3 ranged from weak to strong. In contrast, in the cancer tissues "many of the cancer cells exhibited abundant Id-1, Id-2, and Id-3 immunoreactivity," and Id-1 and Id-2 protein was increased significantly in the cancer cells by comparison to the respective controls, mirroring the overexpression at the mRNA level. Thus, the authors report that in both cell lines and tissue samples, increased mRNA levels leads to an increase in protein overexpression, supporting Applicants' assertion.

Support for Applicants' assertion is also found in an article by Caberlotto *et al.* (Neurosci. Lett. 1999; 256(3):191-4) (abstract attached as Exhibit 9). In a previous study, the authors investigated alterations of neuropeptide Y (NPY) mRNA expression in the Flinders Sensitive Line rats (FSL), an animal model of depression. *Id.* at Abstract. The authors reported that in the current study, that NPY-like immunoreactivity (NPY-LI) was decreased in the hippocampal CA region, and increased in the arcuate nucleus, and that fluoxetine treatment elevated NPY-LI in the arcuate and anterior cingulate cortex. The authors state that "[t]he results demonstrate a good correlation between NPY peptide and mRNA expression." Thus, increases and decreases in mRNA levels were reflected in corresponding changes in protein level.

Mizrachi and Shemesh (Biol. Reprod. 1999; 61(3):776-84) (abstract attached as Exhibit 10) investigated their hypothesis that FSH regulates the bovine cervical prostaglandin E(2) (PGE(2)) synthesis that is known to be associated with cervical relaxation and opening at the time of estrus. *Id.* at Abstract. Cervical tissue from pre-estrous/estrous, luteal, and postovulatory cows were examined for the presence of bovine (b) FSH receptor (R) and its corresponding mRNA. The authors report that bFSHR mRNA in the cervix was maximal during pre-estrus/estrus, and that the level of FSHR protein was significantly higher in pre-estrous/estrous cervix than in other cervical tissues. *Id.* The authors state that "[t]here was a good correlation between the 75-kDa protein expression and its corresponding transcript of 2.55 kb throughout the estrous cycle as described by Northern blot analysis as well as RT-PCR." *Id.* Thus, changes in the level of mRNA for bFSHR led to corresponding changes in FSHR protein levels, a result which supports Applicants' assertion.

In a study by Stein *et al.* (J. Urol. 2000; 164(3 Pt 2):1026-30) (abstract attached as Exhibit 11), the authors studied the role of the regulation of calcium ion homeostasis in smooth muscle contractility. *Id.* at Abstract. The authors investigated the correlation between sarcoplasmic endoplasmic reticulum, calcium, magnesium, adenosine triphosphatase (SERCA) protein and gene expression, and the contractile properties in the same bladder. Partial bladder outlet obstructions were created in adult New Zealand white rabbits, which were divided into control, sham operated and obstructed groups. Stein *et al.* report that "[t]he relative intensities of signals for the Western [protein] and Northern [mRNA] blots demonstrated a strong correlation between protein and gene expression. ... The loss of SERCA protein expression is mediated by down-regulation in gene expression in the same bladder." *Id.* This report supports Applicants' assertion that changes in mRNA level, e.g. a decrease, lead to a corresponding change in the level of the encoded protein, e.g. a decrease.

In an article by Gou and Xie (Zhonghua Jie He He Hu Xi Za Zhi. 2002; 25(6):337-40) (abstract attached as Exhibit 12) the authors investigated the expression of macrophage migration inhibitory factor (MIF) in human acute respiratory distress syndrome(ARDS) by examining the expression of MIF mRNA and protein in lung tissue in ARDS and normal persons. *Id.* at Abstract. The authors report "undetectable or weak MIF mRNA and protein expression in normal lungs. In contrast, there was marked upregulation of MIF mRNA and protein expression in the ARDS lungs." *Id.* This is consistent with Applicants' assertion that a change in mRNA for a particular gene, e.g. an increase, generally leads to a corresponding change in the level of protein expression, e.g. an increase.

These studies are representative of numerous published studies which support Applicants' assertion that changes in mRNA level generally lead to corresponding changes in the level of the expressed protein. Applicants submit herewith an additional 70 references (abstracts attached as Exhibit 13) which support Applicants' assertion.

In addition to these supporting references, Applicants also submit herewith additional references which offer indirect support of Applicants' asserted utility. As discussed in detail above, Applicants have challenged the relevance of references such as Haynes *et al.*, Gygi *et al.*, and Chen *et al.* which do not attempt to examine the correlation between a change in mRNA level and a change in the level of the corresponding protein level. Because the PTO continues to

rely on these references, Applicants are submitting references which report results that are contrary to the PTO's cited references and offer indirect support for Applicants' asserted utility.

For example, in an article by Futcher *et al.* (Mol. Cell Biol. 1999; 19(11):7357-68) (abstract attached as Exhibit 14) the authors conducted a study of mRNA and protein expression in yeast which was nearly identical to the one conducted by Gygi *et al.* and reported in Haynes *et al.* Contrary to the results of the earlier study by Gygi, Futcher *et al.* report "a good correlation between protein abundance, mRNA abundance, and codon bias." *Id.* at Abstract.

In a study which is more closely related to Applicants' asserted utility, Godbout *et al.* (J. Biol. Chem. 1998; 273(33)21161-8) (abstract attached as Exhibit 15) studied the DEAD box gene, DDX1, in retinoblastoma and neuroblastoma tumor cell lines. The authors report that "there is a good correlation with DDX1 gene copy number, DDX1 transcript levels, and DDX1 protein levels in all cell lines studied." *Id.* Thus, in these cancer cell lines, DDX1 mRNA and protein levels are correlated.

Similarly, in an article by Papotti *et al.* (Virchows Arch. 2002; 440(5):461-75) (abstract attached as Exhibit 16) the authors examined the expression of three somatostatin receptors (SSTR) at the mRNA and protein level in forty-six tumors. *Id.* at Abstract. The authors report a "good correlation between RT-PCR [mRNA level] and IHC [protein level] data on SSTR types 2, 3, and 5." *Id.*

Van der Wilt *et al.* (Eur. J. Cancer. 2003; 39(5):691-7) (abstract attached as Exhibit 17) studied deoxycytidine kinase (dCK) in seven cell lines, sixteen acute myeloid leukemia samples, ten human liver samples, and eleven human liver metastases of colorectal cancer origin. *Id.* at Abstract. The authors report that "enzyme activity and protein expression levels of dCK in cell lines were closely related to the mRNA expression levels" and that there was a "good correlation between the different dCK measurements in malignant cells and tumors." *Id.*

Grenback *et al.* (Regul. Pept. 2004; 117(2):127-39) (abstract attached as Exhibit 18) studied the level of galanin in human pituitary adenomas using a specific radioimmunoassay. *Id.* at Abstract. The authors report that "[i]n the tumors analyzed with in situ hybridization there was a good correlation between galanin peptide levels and galanin mRNA expression." *Id.*

Similarly, Shen *et al.* (Blood. 2004; 104(9):2936-9) (abstract attached as Exhibit 19) examined the level of B-cell lymphoma 2 (BCL2) protein expression in germinal center (GC)

B-cells and diffuse large B-cell lymphoma (DLBCL). *Id.* at Abstract. The authors report that "GC cells had low expression commensurate with the low protein expression level" and that in DLBCL the level of BCL2 mRNA and protein expression showed "in general, a good correlation." *Id.*

Likewise, in an article by Fu *et al.* (Blood 2005; 106(13):4315-21) (abstract attached as Exhibit 20) the authors report that six mantle cell lymphomas studied "expressed either cyclin D2 (2 cases) or cyclin D3 (4 cases)." *Id.* at Abstract. "There was a good correlation between cyclin D protein expression and the corresponding mRNA expression levels by gene expression analysis." *Id.*

These examples are only a few of the many references Applicants could cite in rebuttal to the PTO's arguments. Applicants submit herewith 26 additional references (abstracts attached as Exhibit 21) which also support Applicants' assertion in that the references report a correlation between the level of mRNA and corresponding protein, contrary to the assertion of the PTO that mRNA and protein levels are not correlated.

In summary, Applicants submit herewith a total of 113 references and an additional expert Declaration in addition to the declarations and references already of record, which support Applicants' asserted utility, either directly or indirectly. This evidence supports the assertion that in general, a change in mRNA expression level for a particular gene leads to a corresponding change in the level of expression of the encoded protein. As Applicants have previously acknowledged, the correlation between changes in mRNA level and protein level is not exact, and there are exceptions (*see, e.g.,* abstracts attached as Exhibit 22). However, Applicants remind the PTO that the asserted utility does not have to be established to a statistical certainty, or beyond a reasonable doubt. *See M.P.E.P.* at § 2107.02, part VII (2004). Therefore, the fact that there are exceptions to the correlation between changes in mRNA and changes in protein does not provide a proper basis for rejecting Applicants' asserted utility. Applicants submit that considering the evidence as a whole, with the overwhelming majority of the evidence supporting Applicants' asserted utility, a person of skill in the art would conclude that Applicants' asserted utility is "more likely than not true." *Id.*

In conclusion, Applicants submit that they have offered sufficient evidence to establish that it is more likely than not that one of skill in the art would believe that because the PRO1753

mRNA is differentially expressed in esophageal tumors as compared to normal esophageal tissue, the PRO1753 polypeptide will likewise be differentially expressed in esophageal tumors. This differential expression of the PRO1753 polypeptide makes the claimed polypeptides useful as diagnostic tools for cancer, particularly esophageal cancer.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Polypeptides

Applicants next address the PTO's assertion that the asserted utilities are not specific to the claimed polypeptides related to PRO1753. Applicants respectfully disagree.

Specific utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO1753 gene and polypeptide in certain types of tumor cells, along with the declarations and references discussed above, provide a specific utility for the claimed polypeptides.

As discussed above, there are significant data which show that the gene for the PRO1753 polypeptide is differentially expressed by at least two-fold in esophageal tumors as compared to normal esophageal tissue. These data are strong evidence that the PRO1753 gene and polypeptide are associated with esophageal tumors. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the PRO1753 gene and polypeptide with a specific disease. The asserted utility for the claimed polypeptides as diagnostic tools for cancer, particularly esophageal tumors, is a specific utility – it is not a general utility that would apply to the broad class of polypeptides.

Utility – Conclusion

Applicants remind the PTO that the evidence supporting utility does not need to be direct evidence, nor does it need to provide an exact correlation between the submitted evidence and the asserted utility. Instead, evidence which is "reasonably" correlated with the asserted utility is sufficient. *See Fujikawa v. Wattanasin*, 93 F.3d 1559, 1565, 39 U.S.P.Q. 2d 1895 (Fed. Cir. 1996) ("a 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' suffices"); *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed.

Cir. 1985) (same); *Nelson v. Bowler*, 626 F.2d 853, 857, 206 U.S.P.Q. 881 (C.C.P.A. 1980) (same). In addition, utility need only be shown to be "more likely than not true," not to a statistical certainty. *M.P.E.P.* at § 2107.02, part VII (2004). Considering the evidence as a whole in light of the relevant standards for establishing utility, Applicants have established at least one specific, substantial, and credible utility. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejections under 35 U.S.C. § 112, first paragraph – Enablement

The PTO also maintains its rejection of pending Claims 6-8 and 11-17 under 35 U.S.C. § 112, first paragraph. Specifically, the PTO asserts that because the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention. *Final Office Action* at 24. In addition, the PTO asserts that the enablement would not be commensurate in scope with Claims 4-5 and 12-17. *Final Office Action* at 25-27.

The PTO has Failed to Establish a Reasonable Basis to Question the Enablement of the Pending Claims

The PTO has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *See M.P.E.P.* § 2164.04. It is incumbent for the PTO "to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *Id.* (quoting *In re Marzocchi*, 439 F.2d 220, 224, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971). This can be done "by making specific findings of fact, supported by the evidence, and then drawing conclusions based on these findings of fact." *Id.*

As an initial matter, Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed polypeptides. To the extent that the enablement rejection is based on a lack of utility, Applicants respectfully request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. §112.

With respect to Claims 14-17, which recite the limitation "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO: 110 in esophageal tissue samples," the PTO states that "[t]hese claims encompass any and all antigenically cross-reactive polypeptides possessing the recited percent identity, regardless of their biological activity." *Id.* at 26. The PTO continues, arguing:

> If mere antigenic cross-reactivity were the test for enablement under § 112, Applicants could obtain patent rights that may confer power to block off whole areas of scientific development related to the biological activity of the polypeptide, for which Applicants have not provided any disclosure. It is entirely unclear why the disclosure of a single polypeptide, i.e., PRO1753, which is ideally suited to the making of antibodies to itself, would enable any and all antigenically cross-reactive polypeptides possessing the recited percent identity and possessing unknown and undisclosed biological activities, when the specification provides no disclosure of any biological activity. Therefore, the scope of enablement provided to the skilled artisan by the disclosure is not commensurate with the scope of protection sought by the claims. *Id.* at 26-27.

The standard for determining whether the specification meets the enablement requirement is to be evaluated based on whether or not the experimentation needed for one skilled in the art to practice the invention would be undue. *Mineral Separation v. Hyde,* 242 U.S. 261, 270 (1916); *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988); *M.P.E.P.* § 2164.01. Applicants submit that in view of the requirements of enablement under 35 U.S.C. §112, first paragraph, the PTO has failed to establish a *prima facie* basis for rejecting Claims 14-17 as lacking enablement. The PTO's statements fail to establish a reasonable basis to question the enablement provided for the claimed invention. *See M.P.E.P.* § 2164.04.

It is incumbent for the PTO "to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *Id.* (quoting *In re Marzocchi*, 439 F.2d 220, 224, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971). This can be done "by making specific findings of fact, supported by the evidence, and then drawing conclusions based on these findings of fact." *Id.* The PTO has failed to make any specific findings of fact, or back up its assertions with any acceptable evidence or reasoning.

In the present case, the PTO reasons that "[i]f mere antigenic cross-reactivity were the test for enablement under § 112, Applicants could obtain patent rights that may confer power to block off whole areas of scientific development related to the biological activity of the polypeptide, for which Applicants have not provided any disclosure." This is not the test for enablement.

The M.P.E.P. states that "if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention." *M.P.E.P.* § 2164.01(c) (emphasis added). As described above, the specification adequately discloses how to make and use the polypeptides of Claims 14-17. The PTO has not alleged that undue experimentation would be required to practice the claimed invention, only that the claimed scope of the invention is too broad. Accordingly, it remains unquestioned that the claimed polypeptides have an enabled use.

Asserting that "[i]t is entirely unclear why the disclosure of a single polypeptide, ... would enable any and all antigenically cross-reactive polypeptides possessing the recited percent identity and possessing unknown and undisclosed biological activities, when the specification provides no disclosure of any biological activity," is also not a reason to reject the claimed polypeptides as lacking enablement. The subject matter of Claims 14-17 relates to isolated polypeptides with at least 95% identity to the disclosed polypeptides wherein the claimed polypeptides can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO: 110 in esophageal tissue samples. The PTO has not offered any explanation of how the failure to disclose "any biological activity" results in one of skill in the art having to resort to undue experimentation to practice the claimed invention. Disclosure of a "biological activity" is not required for one of skill in the art to either make or use the claimed polypeptides.

Further, "[t]he presence of only one example should never be the sole reason for rejecting claims as being broader than the enabling disclosure, even though it is a factor to be considered along with all the other factors. To make a valid rejection, one must evaluate all the facts and evidence and state why one would not expect to be able to extrapolate that one example across the entire scope of the claims." *M.P.E.P.* § 2164.02. The PTO provides no other basis for rejection of the Claims 14-17 aside from pointing to "disclosure of a single polypeptide."

Accordingly, pointing to the disclosure of a single polypeptide, absent any other evidence, cannot support *prima facia* rejection of lack of enablement of the claimed polypeptides.

Notwithstanding the failure of the PTO to provide sufficient evidence to support a *prima facie* rejection of Claims 14-17, the specification teaches in detail how to make the claimed polypeptides, including variants thereof, and antibodies which specifically bind PRO1753. *See, e.g.,* ¶¶ [0283]-[0315]; [0256]-[0271]; [0361]-[0379]; and Examples 6-10 (¶¶ [0453]-[0499]). In addition, the specification discloses that antibodies to claimed polypeptides can be used in diagnostic assays to detect the expression of PRO1753 in specific types of tissue. *See e.g., Specification* at [0407].

Thus, there is significant guidance how to make and use the claimed polypeptides. In addition, as the disclosure and references cited in the specification make clear, the production of polypeptides, polypeptide variants, and specific antibodies is a predictable and well established aspect of the biological sciences. *See, e.g., In re Wands*, 858 F.2d 731, 8 U.S.P.Q. 2d 1400 (Fed. Cir. 1988) (reversing the Board's decision of non-enablement and holding that as of 1980, undue experimentation was not required to make high-affinity monoclonal antibodies to a target peptide); *Sutcliffe et al.,* Science (1983) 219:660-666 at 661-662 (teaching that "by following simple rules, one can in general select peptides that will elicit antibodies reactive with intact proteins") (attached as Exhibit 23).

In conclusion, the PTO's rejection based on lack of utility has been addressed above, and the PTO has otherwise failed to meet its burden to establish a reasonable basis to question the enablement provided for the claimed invention – unsupported conclusory statements are simply not sufficient. Given the skill in the art and the disclosure of how to make and use the claimed polypeptides, Applicants request that the PTO reconsider and withdraw its rejection under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. §112, first paragraph – Written Description

The PTO maintains the rejection of pending Claims 12-17 under 35 U.S.C. § 112, first paragraph, as failing to satisfy the written description requirement for the reasons set forth in the previous Office Actions. *Final Office Action* at 27.

The PTO has Failed to Meet Its Initial Burden of Rebutting the Presumption that the Pending Claims are Adequately Described

To overcome the presumption that the claimed subject matter is adequately described, the PTO must present "evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *Wertheim*, 541 F.2d at 263, 191 U.S.P.Q. at 97." *M.P.E.P.* § 2163.04. To support its rejection of pending Claims 12-17, the PTO has merely repeated, nearly verbatim, the same arguments made in support of its enablement rejection.

Applicants note that Claims 4 and 5 which recited the limitations at issue have been canceled, and Claim 12, which depended from Claim 4, has been amended to depend from Claim 6. Claims 12-13 as dependent from Claim 6 do not recite percent amino acid sequence identity as a limitation, nor do they recite any limitation regarding overexpression in esophageal tumors. These claims are directed to fusion peptides of the disclosed sequence, with or without the disclosed signal peptide. In the absence of any arguments as to "why one of skill in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims," the PTO has failed to rebut the presumption that the specification satisfies the written description requirement for pending Claims 12-13. *See M.P.E.P.* § 2163.04.

With respect to Claims 14-17, which recite the limitation "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO: 110 in esophageal tissue samples," the PTO repeats its assertion that "[t]hese claims encompass any and all antigenically cross-reactive polypeptides possessing the recited percent identity, regardless of their biological activity." *Id.* at 28. The PTO continues, arguing:

> Applicants have not described the biologic activity of the PRO1753 polypeptide or any of its variants. It is entirely unclear why the disclosure of a single polypeptide, i.e., PRO1753, which is ideally suited to the making of antibodies to itself, would describe any and all antigenically cross-reactive polypeptides possessing the recited percent identity and possessing unknown and undisclosed biological activities, when the specification does not describe any biological activity. *Id.* at 28.

The PTO concludes that as a result, the claimed subject matter is not adequately described. *Id.*

As noted above, "[a] description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption." *M.P.E.P.* § 2163.04 (emphasis added). Therefore "[t]he examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims." *Id.*

The PTO has not provided any reasoning or evidence as to how the absence of the disclosure of "biological activity" results in an inadequate description of the subject matter of Claims 14-17. The claimed subject matter relates to polypeptides that have at least 95% sequence identity to SEQ ID NO:110, and can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO: 110 in esophageal tissue samples. Applicants fail to see how any "biological activity" of the claimed polypeptides, aside from being able to generate an antibody which can specifically detect the polypeptide of SEQ ID NO: 110, is at all relevant to an adequate description of the claimed polypeptides which are not claimed on the basis of any "biological activity." In the absence of any other arguments as to why one of skill in the art would not recognize a description of the claimed invention in Applicants' disclosure, the PTO has failed to rebut the presumption that the specification satisfies the written description requirement for Claims 14-17. *See M.P.E.P.* § 2163.04.

Rejected Claims 12-17 are Adequately Described

The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. *See e.g., Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 U.S.P.Q.2d at 1116 (Fed. Cir. 1991) (emphasis added). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. *Union Oil v. Atlantic Richfield Co.*, 208 F.3d 989, 996 (Fed. Cir. 2000).

Pending claims 12-13, which depend from Claim 6, are adequately described by the specification. Claim 6 is directed to an isolated polypeptide comprising the amino acid sequence of the polypeptide of SEQ ID NO:110, the amino acid sequence of the polypeptide of SEQ ID NO:110 lacking its associated signal peptide, or the amino acid sequence of the polypeptide

encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203535.

As stated above, the PTO provides no basis for rejecting either of pending Claims 12-13 because the PTO's arguments are directed at claims reciting the limitation "wherein said isolated polypeptide is encoded by a polynucleotide that is more highly expressed in esophageal tumor tissue compared to normal esophageal tissue," or "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO: 110 in esophageal tissue samples." *See Final Office Action* at 27-29. As amended, Claims 12-13 depend from Claim 6, which does not recite the objected to limitation.

Regardless of any lack of reasoning provided by the PTO, Applicants assert that each recited element of Claim 6 is explicitly disclosed in the specification, either in writing (*see, e.g., Specification* at Figure 110) or by virtue of a biological deposit. Accordingly, there can be no basis for holding that Claim 6 is not adequately described. Likewise, Claims 12-13, which are drawn to chimeric polypeptides comprising the polypeptide of Claim 6, are also fully described by the specification. As such, Applicants request that the PTO reconsider and withdraw the rejection of Claims 12-13 under 35 U.S.C. § 112, first paragraph, for lack of written description.

Claims 14-17 are also adequately described by the specification. Claim 14 is directed to an isolated polypeptide having at least 95% amino acid sequence identity to the amino acid sequence of the polypeptide SEQ ID NO:110, the amino acid sequence of the polypeptide of SEQ ID NO:110 lacking its associated signal peptide, or the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203535; wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:110 in esophageal tissue samples. Claims 16 and 17 ultimately depend from Claim 14. Similarly, Claim 15 recites "at least 99% amino acid sequence identity."

Applicants maintain that there is no substantial variation within the species which fall within the scope of the rejected claims, which require at least 95% amino acid sequence identity to SEQ ID NO:110 and can be used to generate antibodies which specifically detect the

polypeptide of SEQ ID NO:110 in esophageal tissue samples. As such, Applicants were in possession of the common attributes or features of the claimed subject matter.

The rejected claims are analogous to the claims discussed in Example 14 of the written description training materials available on the PTO's website. In Example 14, the written description requirement was found to be satisfied for claims directed to polypeptides with 95% homology to a disclosed sequence that also possess a recited catalytic activity, where procedures for making variant proteins were routine in the art and the specification provided an assay for detecting the recited catalytic activity of the protein. This disclosure satisfies the written description requirement even though the applicant had disclosed only a single species and had not made any variants. The Guidelines state that "[t]he single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO: 3 which are capable of the specified catalytic activity."

Similarly, the pending claims also have at least 95% or 99% sequence identity to the disclosed sequence, and must be able to generate antibodies which specifically detect the polypeptide of SEQ ID NO:110 in esophageal tissue samples. As in Example 14, at the time of the effective filing date of the instant application, it was well known in the art how to make polypeptides with at least 95% or 99% amino acid sequence identity to the disclosed sequences. *See, e.g., Specification* at ¶¶ [0256]-[0271]. In addition, the specification discloses in detail how to make antibodies which specifically detect a particular PRO polypeptide, and how to use them to detect the PRO polypeptide in a particular tissue. *See, e.g., Specification* ¶¶ [0363]-[0379], [0407], and [0493]-[0499]. Like a particular catalytic activity, the function of being useful to produce an antibody specific to SEQ ID NO:110 is directly related to the structure of the claimed polypeptides. Thus, like Example 14, the genus of polypeptides that have at least 95% amino acid sequence identity to the disclosed sequences and possess the described functional activity are adequately described.

Claims 16 and 17, drawn to particular embodiments of Claim 14, are also fully described by the specification. The PTO does not contest the written description support for any embodiment recited in Claims 16-17.

The PTO asserts that the present claims are not analogous to those discussed in Example 14 of the written description guidelines because the specification does not describe any biological activity of the claimed polypeptides and because the claims are not limited to any specific "biological activity" of the claimed polypeptides. *Final Office Action* at 28-29.

Applicants submit that the applicability of Example 14 is not limited to polypeptides for which the biological function is known and recited, but extends to all situations where the polypeptide is useful and there is no substantial variation within the species encompassed by the claims. The purpose of the recited catalytic activity in the example is to limit the amount of structural variation within the species. The commentary in the Guidelines states that the description of an assay to detect variants which have the recited activity, along with 95% homology, is sufficient to satisfy the written description requirement.

Similarly, in the instant case, Claims 14-17 must share a particular "biological activity" which restricts the amount of permissible structural variation within the species – the claimed polypeptides must be useable to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO: 110 in esophageal tissue samples. This limitation combined with the disclosure of how to make and test the recited antibodies generated from the claimed polypeptides, along with the requirement of least 95% or 99% amino acid sequence identity, results in claimed subject matter where there is no substantial variation within the species encompassed by the claims. Accordingly, Applicants maintain that the pending claims are analogous to the claims in Example 14.

As for the PTO's statement that "[i]t is entirely unclear why the disclosure of a single polypeptide, i.e., PRO1753, ...would describe any and all antigenically cross-reactive polypeptides possessing the recited percent identity," the basic premise that a large genus can not be adequately described by a single species is simply wrong. In a recent Federal Circuit decision, *In re Wallach*, 378 F.3d 1330, 1333-34 (Fed. Cir. 2004), the Court stated:

> [W]e agree with Appellants that the state of the art has developed such that the complete amino acid sequence of a protein may put one in possession of the genus of DNA sequences encoding it, and that one of ordinary skill in the art at the time the '129 application was filed may have therefore been in possession of the entire genus of DNA sequences that can encode the disclosed partial protein sequence, even if individual species within that genus might not have been described or rendered obvious. ... A claim to the genus of DNA molecules complementary to the RNA having the sequences encompassed by that formula, even if defined only

> in terms of the protein sequence that the DNA molecules encode, while containing a large number of species, is definite in scope and provides the public notice required of patent applicants.
>
> ***
>
> Moreover, we see no reason to require a patent applicant to list every possible permutation of the nucleic acid sequences that can encode a particular protein for which the amino acid sequence is disclosed, given the fact that it is, as explained above, a routine matter to convert back and forth between an amino acid sequence and the sequences of the nucleic acid molecules that can encode it. *Id.* (emphasis added).

The Court did not require the applicants in *Wallach* to actually make or individually describe all of the *vast* number of sequences which encode the disclosed protein sequence. This is in spite of the fact that only a single protein sequence was disclosed, and the encompassed genus was enormous due to codon degeneracy in the genetic code – even the most skilled artisan could not individually envision the detailed chemical structure of the nucleic acids encompassed by the claimed genus. The Court reasoned that because it is routine to convert between amino acid sequences and nucleic acid sequences, disclosure of a single amino acid sequence was sufficient to place the applicants in possession of the enormous genus of nucleic acids which could encode the sequence.

The facts in *Wallach* are very similar to the instant case. Here, Applicants have disclosed SEQ ID NO:110, and claim polypeptides which are at least 95% or 99% identical to it and have the functional limitation of the ability to generate antibodies which can be used to specifically detect SEQ ID NO:110 in esophageal tissue samples. As discussed above, it is routine in the art to create polypeptides which have at least 95% or 99% sequence identity to SEQ ID NO:110 – it is just as predictable and easy as creating all of the nucleic acids which encode a particular amino acid sequence. Similarly, it is well within the knowledge of those skilled in the art how to determine which polypeptides can be used to make the recited antibodies. The predictability of this structure/function combination is sufficient to place the claimed subject matter in the possession of the Applicants, and thus the claimed polypeptides are adequately described. The *Wallach* opinion makes clear that there is no need to literally describe more than a single species to adequately describe a large genus where one of skill in the art recognizes that the disclosed species puts the applicant in possession of the claimed genus.

In conclusion, the PTO has failed to meet its "initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims." *M.P.E.P.* § 2163.04. And even if it has met this burden, Applicants submit that they have satisfied the written description requirement for the pending claims based on the actual reduction to practice of SEQ ID NO:110, by specifying a high level of amino acid sequence identity, and by describing how to make antibodies to the disclosed sequence, all of which result in a lack of substantial variability in the species falling within the scope of the instant claims. Applicants submit that this disclosure would allow one of skill in the art to "recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus." Hence, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

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